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09/890,463	11/09/2001	Ove Hoech-Guldberg	Q-65619	3310

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EXAMINER	
ROBINSON, HOPE A	
ART UNIT	PAPER NUMBER
1653	

DATE MAILED: 08/26/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/890,463	HOECH-GULDBERG ET AL.	
	Examiner	Art Unit	
	Hope A. Robinson	1653	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *21 May 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-10 and 17-26* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-10 and 17-26* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *01 August 2001* is/are: a)☐ accepted or b)☒ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Application Status

1. Applicant's election without traverse of Group I (claims 1-10 and 17-26) on May 21, 2004 is acknowledged.

2. The Amendments filed on August 1, 2001 and May 21, 2004 have been received and entered.

Claim Disposition

3. Claims 11-16 and 27-31 have been canceled. Claim 19 has been amended. Claims 1-10 and 17-26 are pending and under examination.

Drawing

4. The Drawings filed on August 1, 2001 are objected to because Figure 2 for example, is blurred, thus, the lanes described are not easy to determine.

Correction is required.

Information Disclosure Statement

5. The Information Disclosure Statement filed on November 9, 2001 has been received and entered. The references cited on the PTO-1449 Form have been considered by the examiner and a copy is attached to the instant Office action.

Abstract

6. The abstract of the disclosure is objected to because at line 8, there appears the range of "300-700 nm" however, the instant specification discloses a range of "350-700 nm", see page 3, lines 10-15, for example.

Correction is required. See MPEP § 608.01(b).

Specification

7. The specification is objected to because of the following informalities:

(a) The specification is objected to because trademarks are disclosed throughout the instant specification and not all of them are capitalized or accompanied by the generic terminology. The use of the trademark such as PROCHECK™, for example, has been noted in this application (see page 12). It should be capitalized wherever it appears and be accompanied by the generic terminology. Although the use of trademarks is permissible in patent applications, the proprietary nature of the marks should be respected and every effort made to prevent their use in any manner, which might adversely affect their validity as trademarks.

(b) The specification is also objected to because the continuity data on page 1 does not include the priority claim to "Australia PP 8463 filed February 2, 1999" (see the amendment filed on August 27, 2001).

(c) The title of the Invention is not descriptive. A new title is required that is clearly indicative of the invention to which the claims are directed. The following is suggested: "Nucleic Acid Encoding Pigment Protein From Coral Tissue".

(d) See also page 4 of the specification at line 36 where there appears "...vectors f the invention...".

(e) See page 22, lines 18-19, for "(231amino acids and 235 amino acids)", where a space is needed between the number of residues and the word "amino".

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

8. Claims 1-10 and 17-26 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The claims are directed to an isolated polynucleotide molecule comprising a nucleotide sequence that encodes a pigment protein from coral, said protein is described as having certain properties such as a specific absorbance spectrum, a specific N-terminal sequence and a chromatophore region comprising QYP. However, the claims do not provide adequate written description because the claims only describe

the claimed polynucleotide by function not by structure tissue (see for example 1-5). According to the MPEP (chapter 2163), "the claimed invention as a whole may not be adequately described if the claims require an essential or critical feature which is not adequately described in the specification and which is not conventional in the art or known to one of ordinary skill in the art". It is also stated that an applicant shows possession of the claimed invention by describing the claimed invention with all of its limitations using such descriptive means as words, structures, figures, diagrams, and formulas that fully set forth the claimed invention. See *Lockwood v. American Airlines, Inc., 107 F.3d 1565, 1572, 41 USPQ2d 1961, 1966 (Fed. Cir.1997)*. Thus, a biomolecule sequence described only by a functional characteristic, without any known or disclosed correlation between that function and the structure of the sequence, normally is not a sufficient identifying characteristic for written description purposes, even when accompanied by a method of obtaining the claimed sequence. For example, even though a genetic code table would correlate to a known amino acid sequence with a genus of coding nucleic acids, the same table cannot predict the native, naturally occurring nucleic acid sequence of a naturally occurring mRNA or its corresponding cDNA.

In addition, claims 6-10 are directed to a genus of polynucleotides. Note that claims 6 and 10 recites the language 'corresponding to' and 'substantially corresponding to' which indicates that the structures claimed encompasses variations, however, the instant specification lacks adequate written description pertaining to the variations. The specification discloses on pages 7-8 that the phrase 'substantially corresponding to' as

used herein in relation to nucleotide sequences is intended to encompass minor variations in the nucleotide sequence which due to degeneracy in the DNA code do not result in a change in the encoded protein and the same definition is provided with regard to the protein sequences. However, this definition is not limiting or explicit because there is no indicia as to what variations are construed as minor that is encompassed in the claimed invention, to allow a skilled artisan to envision the claimed structure and demonstrate possession of the claimed invention. Moreover, it is well known in the prior art that changes in a nucleotide sequence can have a dramatic affect on the protein product encoded by the sequence.

Further, the claims are directed to polynucleotides having at least 80%, 90% or 95% sequence identity with a particular disclosed sequence (see claims 7-9) or that merely hybridizes to a disclosed sequence (see claims 22-26). The specification fails to provide a representative number of species for the claimed genus. A representative number of species means that the species, which are adequately described, are representative of the entire genus. To provide evidence of possession of a claimed genus, the specification must provide sufficient distinguishing identifying characteristics of the genus. *Vas-Cath Inc. v. Mahurkar, 935 F.2d 1555, 1563-64, 19 USPQ2d 1111, 1117 (Fed. Cir.1991)*, states that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in *possession of the invention*. The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed*" (See page 1117). The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed" (See *Vas-*

Cath at page 1116). The skilled artisan cannot envision the detailed chemical structure of the encompassed genus of polynucleotides and the encoded proteins, and therefore, conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method of isolating it. The compound itself is required. *See Fiers v. Revel, 25 USPQ2d 1601 at 1606 (CAFC 1993). See MPEP 2163.* Additionally, the claims are directed to a process for producing the encoded proteins, however, the process steps recited in for example claim 19, is directed to "optionally recovering the expressed protein", which is not demonstrative of possession of the claimed invention.

Note that claims 22-26 are directed to an oligonucleotide probe or primer comprising a nucleotide sequence that hybridizes selectively to a polynucleotide molecule of claim 1, for example. The claims do not set forth what the hybridization conditions are to define the "hybridizes selectively" language. Note that sequences identified by hybridization, would not predictably have the same structural and functional characteristics as the disclosed species because there is no way to determine what variations would be tolerated. Further, there is no indication as to the hybridization conditions used in connection with the claimed invention disclosed in the specification. It is noted that on page 6 of the specification a discussion is provided regarding high stringency conditions, however, there is no discussion regarding "hybridizing selectively", thus this discussion is merely exemplary and not limiting. Therefore, the discussion provided on page 6 does not breathe life into the claims. Further,

hybridization conditions are known in the art to vary, thus the specifications should provide the specific conditions used in the claimed invention to adequately describe the claimed invention. Note also that as the claims depend from claim 1 which recites the phrase "capable of" in association with an activity, that this does not bestow function *per se* to the claimed protein, because "capable of" does not demonstrate possession of a specific function.

Therefore, for all these reasons the specification lacks adequate written description, and one of skill in the art cannot reasonably conclude that the applicant had possession of the claimed invention at the time the instant application was filed.

9. Claims 1-10 and 17-26 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the nucleotides set forth in SEQ ID NO: 5 or 6 for example, encoding proteins set forth in SEQ ID NOS: 3 or 4 for example, does not reasonably provide enablement for any fragments/variants thereof or any nucleic acid probe or primer that hybridizes selectively to the nucleic acid molecule of the claimed invention. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention commensurate in scope with these claims. The enablement requirement refers to the requirement that the specification describe how to make and how to use the invention. There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is undue. These factors

include, but are not limited to: Quantity of experimentation necessary; Amount of direction or guidance presented; Presence or absence of working examples; Nature of the Invention; State of the prior art and Relative skill of those in the art; Predictability or unpredictability of the art and Breadth of the claims (see *In re Wands, 858 F.2d at 737, 8 USPQ2d at1404 (Fed. Cir. 1988)*. The factors most relevant to the instant invention are discussed below.

The amount of experimentation required: The amount of experimentation required to practice the claimed invention is undue as the claims encompass an unspecified amount of fragments/variants of the above claimed sequences. Note that claims 1-5 for example, are directed to an isolated polynucleotide molecule comprising a nucleotide sequence that encodes a pigment protein from coral tissue, said protein is described as having certain properties such as a specific absorbance spectrum, a specific N-terminal sequence and a chromatophore region and no structure is provided for the claimed polynucleotide. Further, the use of the term "capable of" in association with an activity for the encoded protein does not mean that the protein has a definitive function (see claim 1 for example). In addition, claim 1 recites a maximal fluorescence emission range for the encoded protein as being 300 to 700 nm and this range is not supported by the instant specification, which discloses a range of 350-700 (see pages 1 and 3).

Note that claims 6 and 7 for example, provides the structure limitation missing from claim 1, however, the claims encompass variations to the structure with the recitation of the language such as "corresponding to" and the "percent sequence

identity". The specification does not indicate where in the claimed sequences the variations will occur, for example what residues in what positions. The instant specification does not demonstrate or provide guidance as to what the structure of the protein will be once modified or if said protein will be functional or exhibit the same properties or characteristics as the native protein. In the instant application, the partial structure in the form of the recited percent identity is insufficient to determine a chemical structure for the variants encompassed in the claims. Additionally, there is no data provided demonstrative of a particular portion of the structure that must be conserved. Further, as the claims recite the language "capable of emitting fluorescence" which does not demonstrate *per se* that the claimed protein possesses a function, the claims encompass variants/fragments that may not have any biological activity.

Additionally, the claims recite 'hybridizes selectively' (see for example claims 22-26), however, the specific conditions are not recited in the claims or the instant specification. Note that sequences identified by hybridization, would not predictably have the same structural and functional characteristics as the disclosed species because there is no way to determine what variations would be tolerated. For example, Gurskaya et al. (FEBS Letters, vol. 507 (1), pages 16-20, 2001) teach GFP-like chromoproteins and the encoding cDNA, said cDNA has a sequence that is 83.5% identical to the claimed nucleotide sequence set forth in SEQ ID NO:5 (see the alignment attached), which demonstrates that the referenced nucleotide sequence would hybridize. However, the encoded protein of the reference was isolated from a

different genus and species. Further, there is no indication as to the hybridization conditions used in connection with the claimed invention disclosed in the specification.

It is noted that page 6 of the specification provides a discussion of the term 'high stringency', however, does not explicitly define 'selective hybridization'. Therefore the discussion provided does not breathe life into the claims. The mere fact that the hybridization conditions can vary means that the specifications should provide the specific conditions used in the claimed invention to enable one skilled in the art to be able to practice the claimed invention commensurate in scope with the claims. Moreover designing probes or primers which could distinguish a specific sequence from any of the others as broadly encompassed by claim 22 under any given hybridization conditions would require undue experimentation. Due to the large quantity of experimentation necessary to generate the infinite number of variants/fragments recited in the claims and possibly screen same for activity and the lack of guidance/direction provided in the instant specification with regard to the hybridization conditions, this is merely an invitation to the skilled artisan to use the current invention as a starting point for further experimentation. Thus, undue experimentation would be required for a skilled artisan to make and/or use the claimed invention commensurate in scope with the claims.

The high degree of unpredictability in the art: It is well known in the prior art that changes in a nucleotide sequence can have a dramatic affect on the protein product encoded by the sequence. While the degeneracy of the genetic code accommodates some variation in the nucleotide sequence, the extent of variation evident in applicant's claims go far beyond alternate codons for the same amino acid. For example,

Tuddenham et al. (Nucleic Acids Research, vol. 22, no. 17, pages 3511-3533, 1994) discloses databases that demonstrates the deleterious impact that various point mutations, deletions and insertions have on the function of a Factor VIII protein. Tuddenham et al. also demonstrate that a change of only a single nucleotide may result in loss of function in the protein product (see page 3512 of the reference). The reference reports that substitution of an amino acid such as alanine, as a result of the changes to the nucleotide sequence, have a significant functional impact on the polypeptide. The changes to the nucleotide sequence described by Tuddenham et al. are limited in comparison to the wide degree of variability postulated in the instant application (see for example claims 7-9 of the instant application).

In addition, the nucleotide sequence of a nucleic acid probe or primer and the conditions under which the probe or primer is allowed to hybridize are important properties to consider. Predictability of which changes can be made to a nucleic acid probe or primer in combination with the required hybridization conditions for selective hybridization with an expectation of the probe or primer having the ability to selectively hybridize as desired - in this case a nucleic acid encoding a pigment protein from coral tissue that fluoresces in a certain region- is highly unpredictable, particularly in view of the lack of guidance and/or working examples of nucleic acid molecules and probes/primers for this use. Furthermore, even those primers and probes that are identical to, or complementary to a given sequence can detect nucleic acids other than the desired target sequence and, without the necessary guidance for designing probes and primers that selectively detect a specific sequence, it is highly unpredictable as to

whether or not a given probe or primer will have the ability to detect a specific sequence without also detecting other homologous sequences.

The state of the prior art: The state of the prior art provides evidence for the high degree of unpredictability in detecting a specific target nucleic acid using any probe or primer that selectively hybridizes to the nucleic acid molecule. For example, Verploegen et al. (Blood, vol. 96, No. 9, pages 3215-3223, 2000) teach PCR using degenerate primers based on kinase consensus sequences to amplify granulocyte cDNA (page 3216, left column, bottom). The degenerate primers of Verploegen et al. would selectively hybridize to any nucleic acid having the consensus sequence, and would not have the ability to distinguish and detect a desired nucleic acid from other closely related sequences. However, using a probe with a specifically defined nucleotide sequence, Verploegen et al. were able to get the desired results. Thus, in order to detect a desired sequence, one must design a probe or primer such that the probe or primer is specific for the given sequence. Without such specificity, it is highly unpredictable as to whether a given probe or primer has the ability to distinguish a desired nucleic acid from other homologous sequences in a sample.

The lack of guidance and working examples: The specification lacks adequate guidance/direction and working examples to enable a skilled artisan to practice the claimed invention commensurate in scope with the claims. The working examples provided do not rectify the missing information in the instant specification pertaining to the claimed variant (for example, claim 7) or nucleic acids as broadly claimed in claim 22. The specification lacks guidance as to the specific types of variations contemplated,

for example, what residue in what position of what sequence. While it is known in the art that many amino acid substitutions are possible in any given protein, the positions within the protein's sequence where such amino acid substitutions can be made with a reasonable expectation of success are limited, as certain positions in the sequence are critical to the protein's structure/function relationship. Further, the specification fails to provide guidance regarding the design of primers and probes that would selectively detect a specific nucleic acid sequence without also detecting other homologous sequences. Without such guidance for designing and making those probes and primers that would distinguish a single target nucleic acid from other non-specific nucleic acids, one of skill in the art cannot practice the claimed invention as claimed.

The claims are overly broad in scope: The specification does not provide support for the broad scope of the claims, which encompass an unspecified amount of variants/fragments and any nucleic acid probe/primer that selectively hybridizes to the nucleic acid molecule. The claims broadly read on any fragment thereof for the given sequences (SEQ ID NO: 5 or 6 and 3 or 4). The issue in this case is the breath of the claims in light of the predictability of the art as determined by the number of working examples, the skill level artisan and the guidance presented in the instant specification and the prior art of record. This make and test position is inconsistent with the decisions of *In re Fisher, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970)* where it is stated that "...scope of claims must bear a reasonable correlation to scope of enablement provided by the specification to persons of ordinary skill in the art...". Without sufficient guidance, determination of having the desired biological

characteristics is unpredictable and the experimentation left to those skilled in the art is unnecessarily and improperly extensive and undue. See *In re Wands, 858 F.2d at 737, 8 USPQ2d at 1404 (Fed. Cir. 1988)*.

Thus, in view of the overly broad scope of the claims, the lack of guidance and working examples provided in the specification, and the high degree of unpredictability as evidenced by the prior art, undue experimentation would be necessary for a skilled artisan to make and use the entire scope of the claimed invention. In view of the foregoing, applicant has not provided sufficient guidance to enable one of skill in the art to make and use the claimed invention in a manner that reasonably correlates with the scope of the claims, to be considered enabling.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter, which the applicant regards as his invention.

10. Claims 1-2, 5-10 and 17-26 are rejected under 35 U.S.C. 112, second paragraph, as failing to set forth the subject matter, which applicant (s) regard as their invention.

Claim 1 and dependent claims hereto (2, 5-10,17-26) are indefinite for the recitation of "...PPCT capable of emitting fluorescence", because the term "capable of" can be interpreted as "able to" or "equipped", thus it is unclear what else the protein is capable of doing other than fluorescing as the term implies that there are times when the fluorescent activity will not occur. In addition, claim 1 lacks antecedent basis for the

range of "300-700 nm" as the instant specification discloses a range of "350-700 nm", see page 3, lines 10-15, for example.

Claims 7-9 lack antecedent basis as independent claim 1 is directed to a full-length nucleotide sequence and does not recite 80% or 90% or 95% sequence identity.

Claim 19 and the dependent claims hereto (20-21) are indefinite for the recitation of "optionally recovering the expressed protein" because the claims are directed to a "process for producing a pigment protein" and if the protein is not recovered then it is not in hand, and does not meet the objective of the claim.

Claim 22 and the dependent claims hereto (23-26) are indefinite for the recitation of "hybridizes selectively". The phrase is not defined in the specification and it is unclear as to how identical a nucleic acid probe or primer must be to a nucleic acid molecule in order for the probe or primer to "selectively hybridize" thereto.

Art* of *Record

11. The prior art made of record and not relied upon is considered pertinent to applicant's disclosure.

Norris et al. (Plant Molecular Biology, vol. 24, pages 673-677, 1994) teach a nucleotide sequence of a cDNA clone encoding the precursor of peridinin-chlorophyll a-binding protein from the dinoflagellate *Symbiodinium sp.* Isolated from the staghorn coral *Acropora Formosa*, however, the reference does not teach the claimed properties of the encoded protein and the desired region that fluoresces, or the specifically claimed polynucleotide.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Hope A. Robinson whose telephone number is 571-272-0957. The examiner can normally be reached on Monday-Friday from 9:00 a.m. to 6:30 p.m.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jon P. Weber, can be reached at (571) 272-0925.

The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Hope Robinson, MS
Patent Examiner 5/20/04